Reply to: "Might some of the beneficial effects of the Mediterranean diet on non-alcoholic fatty liver disease be mediated by reduced iron stores?"

Reduction of iron stores: An additional potential benefit of the Mediterranean diet in non-alcoholic fatty liver disease?

To the Editor:

We thank Mascitelli *et al.* for their comments regarding our study on the effects of the Mediterranean diet on hepatic steatosis and insulin sensitivity [1]. Mascitelli suggests that because of the relatively low red meat content of the Mediterranean diet (MD), there is a relatively reduced intake of iron, which may be a potential mechanism improving insulin sensitivity and steatosis. We believe that although there is merit in the comments, we would like to dispute some of the statements made.

Firstly, Mascitelli and colleagues state that serum ferritin is a good marker of iron stores in NAFLD. We suggest that whilst in healthy non-diabetic subjects, serum ferritin is strongly associated with hepatic iron stores, in NAFLD this is not the case. In fact, dysmetabolic subjects often have high serum ferritin levels, being the so-called dysmetabolic hyperferritinaemia (DHF) the commonest cause of mild to moderate hyperferritinaemia in clinical practice [2]. As non-alcoholic fatty liver disease (NAFLD) is associated with systemic inflammation, increased adipokine release and oxidative and endoplasmic reticulum stress, the assessment of iron status is particularly challenging in these patients.

However, we agree that hyperferritinaemia has been associated with hepatic histological damage in NAFLD [3]. A recent paper published by the Non-alcoholic Steatohepatitis Clinical Research Network (NASH CRN) demonstrated that in subjects with NASH, a serum ferritin >1.5 × ULN was associated with increased iron deposition, but was also independently associated with a higher NAFLD activity score (NAS) and was a predictor of advanced fibrosis regardless of iron deposition [4].

Hyperferritinaemia is also known to be associated with reduced insulin sensitivity. It is a predictor of development of type 2 diabetes, as well as more rapid progression of cardiovascular disease [5]. In another study, both serum ferritin and hepcidin levels increased linearly with the number of metabolic syndrome features [6]. Therefore, it is likely that the hyperferritinaemia seen in NASH is reflective of reduced insulin sensitivity and the presence of the metabolic syndrome rather than of iron overload. However, it is still unclear which is the nature of the relationship between iron and insulin sensitivity: is ferritin reflective of pathological iron levels that affect IGF-1/insulin signaling [7], or is it simply a marker of the subsequent inflammation and cytokine release that accompanies insulin resistance?

Our subjects underwent baseline ferritin estimations but not follow-up assays, so we can only provide cross-sectional data. Overall, there was no significant association between serum iron and hepatic fibrosis or NAS score, however, this may be because of the small numbers involved.

In our dietary intervention, subjects were exposed to four-week diets. We doubt that this would provide sufficient time for the iron stores to be altered to a sufficient degree as to make any difference to insulin sensitivity or steatosis. However, we also noted that in a recent paper by Kowdley *et al.* [8], the negative effects of iron in an animal model were ameliorated by oleic acid, which was abundant in the diet studied in our paper, providing an additional potential mechanism by which our diet could have reduced insulin sensitivity and steatosis. Overall, we agree that Mascitelli and colleagues provide evidence for an intriguing alternative benefit of the Mediterranean diet in NAFLD.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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